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TITLE OF THE INVENTION (280 characters max)

NOVEL M3 MUSCARINIC ACETLYCHOLINE RECEPTOR ANTAGONISTS

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ENCLOSED APPLICATION PARTS (check all that apply)

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Soma G. Simon

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☐ Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

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20462

CUSTOMER NUMBER

Nov l M_3 Muscarinic Acetylcholin R c ptor Antagonists

FIELD OF THE INVENTION

This invention relates to novel derivatives of cyclic quaternary ammonium salts, pharmaceutical compositions, processes for their preparation, and use thereof in treating M_3 muscarinic acetylcholine receptor mediated diseases.

BACKGROUND OF THE INVENTION

Acetylcholine released from cholinergic neurons in the peripheral and central nervous systems affects many different biological processes through interaction with two major classes of acetylcholine receptors – the nicotinic and the muscarinic acetylcholine receptors. Muscarinic acetylcholine receptors (mAChRs) belong to the superfamily of G-protein coupled receptors that have seven transmembrane domains. There are five subtypes of mAChRs, termed M_1-M_5, and each is the product of a distinct gene. Each of these five subtypes displays unique pharmacological properties. Muscarinic acetylcholine receptors are widely distributed in vertebrate organs, and these receptors can mediate both inhibitory and excitatory actions. For example, in smooth muscle found in the airways, bladder and gastrointestinal tract, M_3 mAChRs mediate contractile responses. For review, please see {Brown 1989 247 /id}.

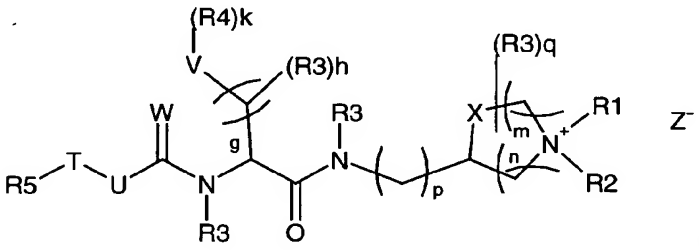
Muscarinic acetylcholine receptor dysfunction has been noted in a variety of different pathophysiological states. For instance, in asthma and chronic obstructive pulmonary disease (COPD), inflammatory conditions lead to loss of inhibitory M_2 muscarinic acetylcholine autoreceptor function on parasympathetic nerves supplying the pulmonary smooth muscle, causing increased acetylcholine release following vagal nerve stimulation. This mAChR dysfunction results in airway hyperreactivity mediated by increased stimulation of M_3 mAChRs{Costello, Evans, et al. 1999 72 /id}{Minette, Lammers, et al. 1989 248 /id}. Similarly, inflammation of the gastrointestinal tract in inflammatory bowel disease (IBD) results in M_3

mAChR-mediated hypermotility {Oprins, Meijer, et al. 2000 245 /id}. Incontinence due to bladder hypercontractility has also been demonstrated to be mediated through increased stimulation of M_3 mAChRs {Hegde & Eglen 1999 251 /id}. Thus the identification of subtytpe-selective mAChR antagonists may be useful as therapeutics in these mAChR-mediated diseases.

Despite the large body of evidence supporting the use of anti-muscarinic receptor therapy for treatment of a variety of disease states, relatively few anti-muscarinic compounds are in use in the clinic. Thus, there remains a need for novel compounds that are capable of causing blockade at M_3 mAChRs. Conditions associated with an increase in stimulation of M_3 mAChRs, such as asthma, COPD, IBD and urinary incontinence would benefit by compounds that are inhibitors of mAChR binding.

SUMMARY OF THE INVENTION

This invention relates to compounds of Formula I



(I)

wherein

When X is carbon, n is 1, 2, or 3; m is 1, 2, or 3; p is 0, 1, or 2;

When X is oxygen, n is 1; m is 2; p is 1 or 2;

W is O, S, or NH;

U is NR3, O, or a bond;

R3 is selected from the group consisting of hydrogen, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, unsubstituted or substituted phenyl, or unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted

by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl and C_3-C_8 cycloalkyl lower alkyl;

q is an interger from 0 to 7;

h is 0, 1, or 2;

g is 1, 2, or 3;

Z^- is selected from the group consisting of I^-, Br^-, Cl^-, F^-, $CF3COO^-$, mesylate, tosylate, and any other pharmaceutically acceptable counter ion;

V is selected from the group consisting of phenyl, thiophenyl, furanyl, pyridinyl, naphthyl, quinolinyl, indolyl, benzothiophenyl and benzofuranyl;

R4 is selected from the group consisting of hydrogen, hydroxy, amino, halo, cyano, trifluoromethyl, C_1-C_8 alkoxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, COR6, COOR6, CONHR6, CON(R6)2, NHR6, N(R6)2, and G;

k is an integer from 0 to 5;

T is selected from the group consisting of an unsubstituted or substituted following group: phenyl, thiophenyl, furanyl, pyridinyl, naphthyl, quinolinyl, indolyl, benzothiophenyl, or benzofuranyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R5 is selected from the group consisting of COOR6, CONHR6, COR6, CON(R6)2, COG, unsubstituted or substituted oxadiazolyl, unsubstituted or substituted oxazolyl, unsubstituted or substituted imidazolyl, unsubstituted or substituted phenoxy, or cyano; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl, C_1-C_8 alkoxy, halo, hydroxy, amino, cyano and trifluoromethyl;

R6 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted phenyl C1-C3 lower alkyl, unsubstituted or substituted naphthyl, or unsubstituted or substituted naphthyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

G is selected from the group consisting of an unsubstituted or substituted following group: pyrrolidinyl, piperdinyl, dihydroindolyl, tetrohydroquinolinyl, morpholino, azetidinyl, hexahydroazepinyl, or octahydroazocinyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, hydroxy, amino, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R1 is selected from the group consisting of an unsubstituted or substituted following group: phenyl, phenyl C1-C6 lower alkyl, thiophenyl, thiophenyl C1-C6 lower alkyl, furanyl, furanyl C1-C6 lower alkyl, pyridinyl, pyridinyl C1-C6 lower alkyl, imidazolyl, imidazolyl C1-C6 lower alkyl, naphthyl, naphthyl C1-C6 lower alkyl, quinolinyl, quinolinyl C1-C6 lower alkyl, indolyl, indolyl C1-C6 lower alkyl, benzothiophenyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl, benzofuranyl C1-C6 lower alkyl, benzoimidazolyl, benzoimidazolyl C1-C6 lower alkyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl C_1-C_6 lower alkyl, or C_3-C_8 alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, phenoxy, phenyl C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower

alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl, pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinolinyl, quinolinyl C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl, benzothiophenyl, benzothiophenyl C1-C3 lower alkyl, benzofuranyl, benzofuranyl C1-C3 lower alkyl, COOH, COR6, COOR6, CONHR6, CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6, OCONHR6, NHCOR6, N(R6)COR6, NHCOOR6 and NHCONHR6;

R2 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, C_3-C_8 alkenyl, unsubstituted or substituted phenyl, or unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

or R1 and R2 is an unsubstituted or substituted following group:

$-(CH_2)_j-$, or $-(CH_2)_i$-Phenyl-$(CH_2)_i-$; wherein, j is an interger from 3 to 8; i is an integer from 1 to 3; when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl.

DETAILED DESCRIPTION

The present invention includes all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds that release the active parent drug according to Formula I **in vivo**. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered

herein. Inventive compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

The meaning of any substituent at any one occurrence in Formula I or any subformula thereof is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of the present invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in **Eur. J. Biochem.**, 158, 9 (1984).

The term "C_1-C_8 alkyl" and "C_1-C_6 alkyl" is used herein includes both straight or branched chain radicals of 1 to 6 or 8 carbon atoms. By example this term includes, but is not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, *tert*-butyl, pentyl, hexyl, heptyl, octyl and the like. "Lower alkyl" has the same meaning as C_1-C_8 alkyl.

Herein "C_1-C_8 alkoxy" includes straight and branched chain radicals of the likes of -O-CH_3, -O-CH_2CH_3, and the n-propoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy, *tert*-butoxy, pentoxy, and hexoxy, and the like.

"C_3-C_8-cycloalkyl" as applied herein is meant to include substituted and unsubstituted cyclopropane, cyclobutane, cyclopentane and cyclohexane, and the like.

"Halogen" or "halo" means F, Cl, Br, and I.

The preferred compounds of Formula I include those compounds wherein:

When X is carbon, n is 1, 2, or 3; m is 1, 2, or 3; p is 0, or 1;

When X is oxygen, n is 1; m is 2; p is 1;

W is O;

U is NR3;

R3 is selected from the group consisting of hydrogen, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, or phenyl C1-C3 lower alkyl;

q is 0;

h is 0;

g is 1;

Z^- is selected from the group consisting of I^-, Br^-, Cl^-, F^-, $CF3COO^-$, mesylate, tosylate, or any other pharmaceutically acceptable counter ion;

V is selected from the group consisting of phenyl, thiophenyl, furanyl, naphthyl, benzothiophenyl or benzofuranyl;

R4 is selected from the group consisting of hydrogen, hydroxy, amino, halo, cyano, trifluoromethyl, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, phenylcarbonyl;

k is 1, 2, 3, 4, or 5;

T is selected from the group consisting of an unsubstituted or substituted following group: phenyl, thiophenyl, furanyl, naphthyl, benzo-thiophenyl, or benzofuranyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R5 is selected from the group consisting of COOR6, CONHR6, COR6, CON(R6)2, COG, unsubstituted or substituted oxadiazolyl, unsubstituted or substituted phenoxy, or cyano; wherein, when substituted, a

group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl and trifluoromethyl;

R6 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, naphthyl, or naphthyl C1-C3 lower alkyl;

G is selected from the group consisting of pyrrolidinyl, piperdinyl, dihydroindolyl, tetrohydroquinolinyl, morpholino, azetidinyl, hexahydroazepinyl, or octahydroazocinyl;

R1 is selected from the group consisting of an unsubstituted or substituted following group: phenyl C1-C6 lower alkyl, thiophenyl C1-C6 lower alkyl, furanyl C1-C6 lower alkyl, pyridinyl C1-C6 lower alkyl, imidazolyl C1-C6 lower alkyl, naphthyl C1-C6 lower alkyl, quinolinyl C1-C6 lower alkyl, indolyl C1-C6 lower alkyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl C1-C6 lower alkyl, benzoimidazolyl C1-C6 lower alkyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl C_1-C_6 lower alkyl, or C_3-C_8 alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, phenoxy, phenyl C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl, pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinolinyl, quinolinyl C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl, benzothiophenyl, benzothiophenyl C1-C3 lower alkyl, benzofuranyl, benzofuranyl C1-C3 lower alkyl, COOH, COR6, COOR6, CONHR6, CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6, OCONHR6, NHCOR6, N(R6)COR6, NHCOOR6 and NHCONHR6;

R2 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, C_3-C_8 alkenyl, or unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

or R1 and R2 is $-(CH_2)_j-$, or $-(CH_2)_i$-Phenyl-$(CH_2)_i-$; wherein, j is an interger from 3 to 8; i is an integer from 1 to 3.

Even more preferred are those compounds where:

X is carbon;

n is 1, or 2;

m is 1, 2, or 3;

p is 0, or 1;

W is O;

U is NR3;

R3 is hydrogen;

q is 0;

h is 0;

g is 1;

Z^- is selected from the group consisting of I^-, Br^-, Cl^-, F^-, $CF3COO^-$, mesylate, tosylate, or any other pharmaceutically acceptable counter ion;

V is selected from the group consisting of phenyl, or naphthyl;

R4 is selected from the group consisting of hydroxy, amino, halo, cyano, trifluoromethyl, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, phenylcarbonyl;

k is 1, 2, or 3;

T is selected from the group consisting of unsubstituted or substituted phenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy,

amino, trifluoromethyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R5 is COOR6, CONHR6, COR6, CON(R6)2, COG, unsubstituted or substituted oxadiazolyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R6 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, or C_3-C_8 cycloalkyl lower alkyl;

G is selected from the group consisting of pyrrolidinyl, piperdinyl, dihydroindolyl, tetrohydroquinolinyl, morpholino, azetidinyl, hexahydroazepinyl, or octahydroazocinyl;

R1 is selected from the group consisting of an unsubstituted or substituted following group: phenyl C1-C6 lower alkyl, thiophenyl C1-C6 lower alkyl, furanyl C1-C6 lower alkyl, pyridinyl C1-C6 lower alkyl, imidazolyl C1-C6 lower alkyl, naphthyl C1-C6 lower alkyl, quinolinyl C1-C6 lower alkyl, indolyl C1-C6 lower alkyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl C1-C6 lower alkyl, benzoimidazolyl C1-C6 lower alkyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl C_1-C_6 lower alkyl, or C_3-C_8 alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, phenoxy, phenyl C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl, pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinolinyl, quinolinyl C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl, benzothiophenyl, benzothiophenyl C1-C3 lower alkyl, benzofuranyl, benzofuranyl C1-C3 lower

alkyl, COOH, COR6, COOR6, CONHR6, CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6 and NHCOR6;

R2 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, or C_3-C_8 alkenyl;

or R1 and R2 is $-(CH_2)_j-$, or $-(CH_2)_i$-Phenyl-$(CH_2)_i-$; wherein, j is an interger from 3 to 7; i is an integer from 1 to 2.

The preferred compounds are selected from the group consisting of:

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{1-[(4-hydroxyphenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{1-[(4-fluorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(4-hydroxyphenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(cyclopropylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-pyrrolidiniumyl)-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-(1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[1-(cyclopropylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-{[1-(cyclopropylmethyl)-1-methyl-4-piperidiniumyl]methyl}-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(3-fluorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-cyanophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[4-(acetylamino)phenyl]methyl}-1-methyl-3-pyrrolidiniumyl)-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(1*R*,3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(1*S*,3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[(1*R*,3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[(1*S*,3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-4-chloro-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-phenylalaninamide trifluoroacetate;

(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-{[*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-3-(2-naphthalenyl)-L-alanyl]amino}-1-methylpyrrolidinium trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-4-(phenylcarbonyl)-L-phenylalaninamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-4-fluoro-L-phenylalaninamide trifluoroacetate;

(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-[((2*S*)-3-(4-biphenylyl)-2-{[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]amino}propanoyl)amino]-1-methylpyrrolidinium trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-4-methyl-L-phenylalaninamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-4-bromo-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-phenylalaninamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-3-chloro-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-phenylalaninamide trifluoroacetate;

4-amino-*N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-phenylalaninamide trifluoroacetate;

N-{(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-chlorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-pyrrolidiniumyl)-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-chlorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

(2*S*)-2-({*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosyl}amino)-5-azoniaspiro[4.5]decane trifluoroacetate;

(3'*S*)-3'-({*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosyl}amino)-1,3-dihydrospiro[isoindole-2,1'-pyrrolidine] trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-pyrrolidiniumyl)-*N*-[({4-[(cyclopropylamino)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-ethyl-1-[(4-fluorophenyl)methyl]-3-pyrrolidiniumyl}-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(4-fluorophenyl)methyl]-1-propyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-(2-propen-1-yl)-3-pyrrolidiniumyl]-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-{[(4-butanoylphenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;
N-[(2*S*)-5-azoniaspiro[4.4]non-2-yl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;
(2*S*)-2-({*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosyl}amino)-5-azoniaspiro[4.6]undecane trifluoroacetate;
N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;
N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[({4-[(methyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;
N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;
N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;
N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[({4-[(propyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;
N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-({[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;
N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-({[4-(5-ethyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;
N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-({[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;
N-{(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-chlorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(cyclopropylmethyl)-1-methyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-({[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-({[4-(5-ethyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-({[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-({[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-({[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-({[4-(5-ethyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-*N*-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1,1-bis(cyclopropylmethyl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1,1-bis(cyclopropylmethyl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

(2*S*)-2-[(*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosyl)amino]-6-azoniaspiro[5.6]dodecane trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-propyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-propyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-propyl-3-piperidiniumyl)-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-propyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-propyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-propyl-3-piperidiniumyl)-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-hydroxyphenyl)methyl]-1-propyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(cyclopropylmethyl)-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(cyclopropylmethyl)-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(cyclopropylmethyl)-1-propyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(cyclopropylmethyl)-1-propyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-({[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-({[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-({[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-({[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-L-tyrosinamide trifluoroacetate; and

N-[(3*S*)-1-(cyclopropylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

or any other pharmaceutically acceptable salt.

The most preferred compounds are selected from the group consisting of:

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[({4-[(propyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;
N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-({[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;
N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-({[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;
N-{(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;
N-{(3*S*)-1-[(4-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;
N-{(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;
N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;
N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;
N-{(3*S*)-1-[(4-chlorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;
N-[(3*S*)-1-(cyclopropylmethyl)-1-methyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;
N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-({[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-({[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-({[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-({[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-({[4-(5-ethyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-*N*-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1,1-bis(cyclopropylmethyl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1,1-bis(cyclopropylmethyl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

(2*S*)-2-[(*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosyl)amino]-6-azoniaspiro[5.6]dodecane trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-propyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-propyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-propyl-3-piperidiniumyl)-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-propyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-propyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-propyl-3-piperidiniumyl)-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-

methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-hydroxyphenyl)methyl]-1-propyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-L-tyrosinamide trifluoroacetate; and

N-[(3*S*)-1-(cyclopropylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

or any other pharmaceutically acceptable salt.

M thods of Preparation

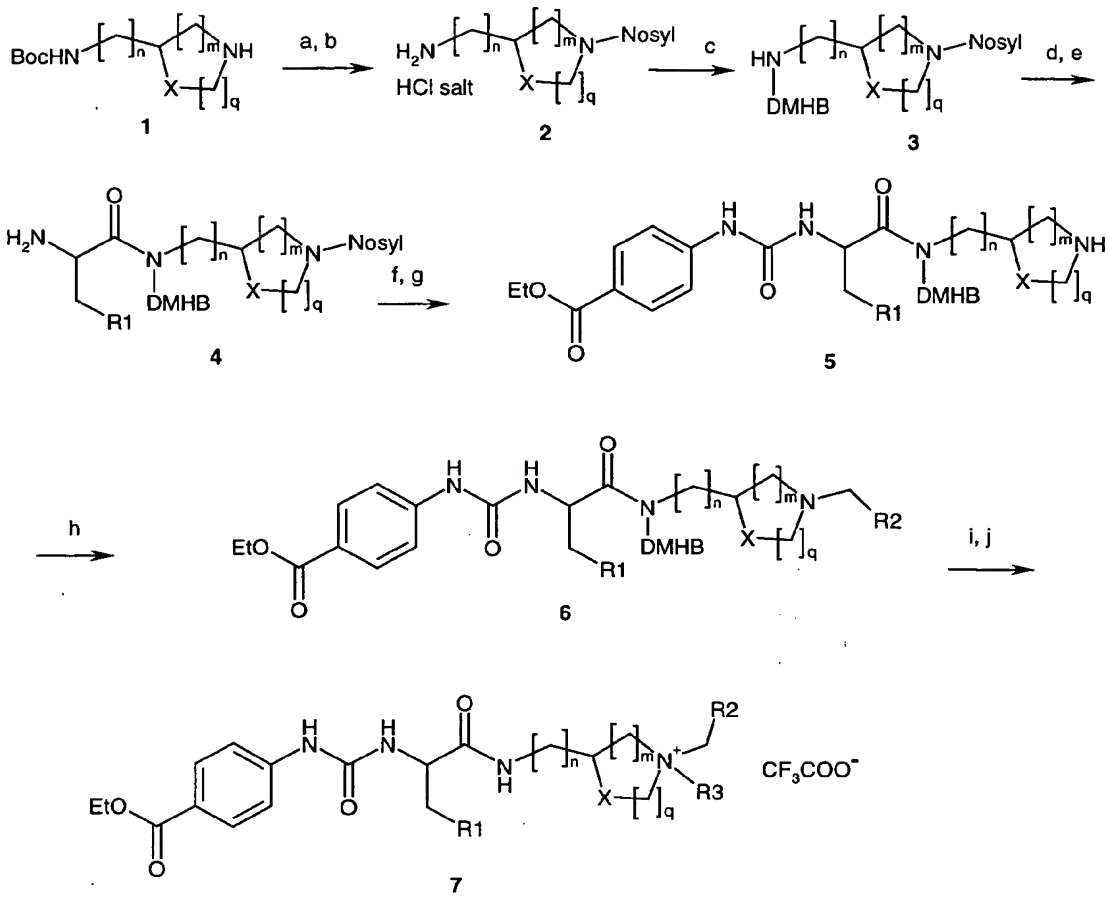
Preparation

The compounds of Formula (I) may be obtained by applying synthetic procedures, some of which are illustrated in the Schemes below. The synthesis provided for these Schemes is applicable for producing compounds of Formula (I) having a variety of different R1, R2, R3, R4, R5 and R6, which are reacted, employing substituents which are suitable protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. While some Schemes are shown with specific compounds, this is merely for illustration purpose only.

Preparation 1

Resin-bound amines **3** were prepared by reductive alkylation of 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) with N-protected diamine HCl salts **2**, which were prepared from Boc-protected diamines **1** (Scheme 1). Reactions of **3** with Fmoc-protected amino acids, followed by removal of the protecting group, provided resin-bound intermediates **4**. Reactions of **4** with isocyanates afforded the corresponding resin-bound ureas, which were subsequently treated with potassium carbonate and thiophenol to give secondary amines **5**. Reductive alkylation of **5** with aldehydes produced resin-bound tertiary amines **6**. Amines **6** were then reacted with alkyl halides (R3Z) to give the corresponding resin-bound quaternary ammonium salts, which were treated with 50% trifluoroacetic acid in 1,2-dichloroethane to afford targeted compounds **7**.

Scheme 1



Conditions: a) 2-nitrobenzenesulfonyl chloride (Nosyl-Cl), pyridine, CH_2Cl_2, 0 °C – rt; b) 4 M HCl in1,4-dioxane, MeOH, rt; c) 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin), $Na(OAc)_3BH$, diisopropylethylamine, 10% acetic acid in 1-methyl-2-pyrrolidinone, rt; d) Fmoc-protected amino acids, 1,3-diisopropylcarbodiimide, 1-hydroxy-7-azabenzotriazole, 1-methyl-2-pyrrolidinone, rt; e) 20% piperidine in 1-methyl-2-pyrrolidinone, rt; f) Ethyl 4-isocyanatobenzoate, 1,2-dichloroethane, rt; g) K_2CO_3, PhSH, 1-methyl-2-pyrrolidinone, rt; h) R2CHO, $Na(OAc)_3BH$, 10% acetic acid in 1-methyl-2-pyrrolidinone, rt; i) R3Z, acetonitrile, rt; j) 50% trifluoroacetic acid in 1,2-dichloroethane, rt.

The following examples are provided as illustrative of the present invention but not limiting in any way:

Exampl 1

Preparation of *N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(4-hydroxyphenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate

a) 3(*S*)-amino-N-(2-nitrobenzenesulfonyl)pyrrolidine HCl salt

To a solution of 3(*S*)-(-)-(*tert*-butoxycarbonyl-amino)pyrrolidine (20.12 g, 108 mmol) in 250 mL of anhydrous methylene chloride at 0 °C was added 13.1 mL (162 mmol) of anhydrous pyridine, followed by slow addition of 25.2 g (113.4 mmol) of 2-nitrobenzenesulfonyl chloride. The mixture was warmed to rt over 1 h and stirred at rt for 16 h. The mixture was poured into 300 mL of 1 M aqueous $NaHCO_3$ solution. After the resulting mixture was stirred at rt for 30 min, the organic layer was separated and washed with 500 mL of 1N aqueous HCl solution twice. The resulting organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used for the the next step without further purification.

To a mixture of the above residue in 140 mL of anhydrous MeOH was added 136 mL (544 mmol) of 4 M HCl in 1,4-dioxane solution. The mixture was stirred at rt for 16 h, concentrated *in vacuo* and further dried in vaccum oven at 35 °C for 24 h to yield 3(*S*)-amino-N-(2-nitrobenzenesulfonyl) pyrrolidine HCl salt as a yellow solid (30.5 g, 92% over the two steps): ^1H NMR (400 MHz, d_6-DMSO) δ 8.63 (s, 3 H), 8.08-7.98 (m, 2 H), 7.96-7.83 (m, 2 H), 3.88-3.77 (m, 1 H), 3.66-3.56 (m, 2 H), 3.46-3.35 (m, 2 H), 2.28-2.16 (m, 1 H), 2.07-1.96 (m, 1 H).

b) DMHB resin bound *O*-(1,1-dimethylethyl)-*N*-{(3*S*)-1-[(2-nitrophenyl)sulfonyl]-3-pyrrolidinyl}-L-tyrosinamide

To a mixture of 7.20 g (10.37 mmol, 1.44 mmol/g) of 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) in 156 mL of 10% acetic

acid in anhydrous 1-methyl-2-pyrrolidinone was added 9.56 g (31.1 mmol) of example **1a** and 9.03 mL (51.84 mmol) of diisopropylethyl amine, followed by addition of 11.0 g (51.84 mmol) of sodium triacetoxyborohydride. After the resulting mixture was shaken at rt for 72 h, the resin was washed with DMF (3 x 250 mL), CH_2Cl_2/MeOH (1:1, 3 x 250 mL) and MeOH (3 x 250 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. Elemental analysis N: 4.16, S: 3.12.

To a mixture of 800 mg (0.860 mmol, 1.075 mmol/g) of the above resin in 15 mL of anhydrous 1-methyl-2-pyrrolidinone was added 1.98 g (4.30 mmol) of Fmoc-Try(tBu)-OH and 117 mg (0.86 mmol) of 1-hydroxy-7-azabenzotriazole, followed by addition of 0.82 mL (5.16 mmol) of 1,3-diisopropylcarbodiimide. After the resulting mixture was shaken at rt for 24 h, the resin was washed with DMF (3 x 25 mL), CH_2Cl_2/MeOH (1:1, 3 x 25 mL) and MeOH (3 x 25 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 657 $[M+H\text{-}tBu]^+$.

The above resin (0.860 mmol) was treated with 15 mL of 20% piperidine in anhydrous 1-methyl-2-pyrrolidinone solution. After the mixture was shaken at rt for 15 min, the solution was drained and another 15 mL of 20% piperidine in anhydrous 1-methyl-2-pyrrolidinone solution was added. The mixture was shaken at rt for another 15 min. The solution was drained and the resin was washed with DMF (3 x 25 mL), CH_2Cl_2/MeOH (1:1, 3 x 25 mL) and MeOH (3 x 25 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h to afford DHMB resin bound *O*-(1,1-dimethylethyl)-*N*-{(3*S*)-1-[(2-nitrophenyl)sulfonyl]-3-pyrrolidinyl}-L-tyrosinamide (0.86 mmol). An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 435 $[M+H\text{-}tBu]^+$.

c) DMHB resin-bound ethyl 4-{[({(1*S*)-1-({4-[(1,1-dimethylethyl)oxy]phenyl}methyl)-2-oxo-2-[(3*S*)-3-pyrrolidinylamino]ethyl}amino)carbonyl]amino}benzoate

To a mixture of 200 mg (0.192 mmol, 0.959 mmol/g) of the above dry resin **1b** in 5 mL of anhydrous 1,2-dichloroethane was added 183.4 mg (0.959 mmol) of ethyl 4-isocyanatobenzoate. After the resulting mixture was shaken at rt for 24 h, the resin was washed with DMF (3 x 10 mL), CH_2Cl_2/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 626 $[M+H\text{-}tBu]^+$.

To a mixture of the above dry resin (0.192 mmol) in 6.4 mL of 1-methyl-2-pyrrolidinone was added 265 mg (1.92 mmol) of K_2CO_3 and 0.0985 mL (0.96 mmol) of PhSH. After the resulting mixture was shaken at rt for 2 h, the resin was washed with DMF (3 x 10 mL), H_2O (3 x 10 mL), DMF (3 x 10 mL), CH_2Cl_2/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h to afford DMHB resin-bound ethyl 4-{[({(1*S*)-1-({4-[(1,1-dimethylethyl)oxy]phenyl}methyl)-2-oxo-2-[(3*S*)-3-pyrrolidinylamino]ethyl}amino)carbonyl]amino}benzoate (0.192 mmol). An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 441 $[M+H\text{-}tBu]^+$.

d) *N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(4-hydroxyphenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate

To a mixture of the above dry resin **1c** (0.192 mmol) in 6.4 mL of 10% HOAc in anhydrous 1-methyl-2-pyrrolidinone solution was added 234 mg (1.918 mmol) of 4-hydroxybenzaldehyde and 407 mg (1.92 mmol) of sodium triacetoxyborohydride. After the resulting mixture was shaken at rt for 72 h,

the resin was washed with DMF (3 x 10 mL), CH_2Cl_2/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 547 $[M+H-tBu]^+$.

To a mixture of the above dry resin (0.192 mmol) in 6.4 mL of anhydrous acetonitrile was added 120 µL (1.918 mmol) of iodomethane. After the mixture was shaken at rt for 16 h, the resin was washed with DMF (3 x 10 mL), CH_2Cl_2/MeOH (1:1, 3 x 10 mL), MeOH (3 x 10 mL) and CH_2Cl_2 (3x10mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. The dry resin was treated with 4 mL of 50% trifluoroacetic acid in dichloroethane at rt for 2h. After the cleavage solution was collected, the resin was treated with another 4 mL of 50% trifluoroacetic acid in dichloroethane at rt for 10min. The combined cleavage solutions were concentrated *in vacuo*. The residue was purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce *N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(4-hydroxyphenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate (white powder, 76 mg, 57% over 10 steps): MS (ESI) 561 $[M]^+$.

Proceeding in a similar manner, but replacing 3(*S*)-(-)-(*tert*-butoxycarbonyl-amino)pyrrolidine with the appropriate Boc-protected diamines and/or replacing 4-hydroxybenzaldehyde with the appropriate aldehydes, the compounds listed in Tables 1 - 12 were prepared.

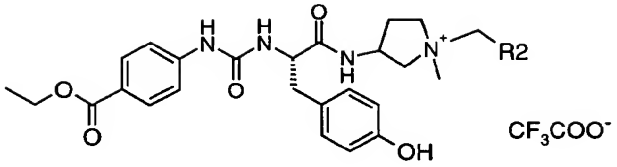


Table 1

Example	R2	MS [M]+
2	4-hydroxy phenyl	561
3	4-cyano phenyl	570
4	4-fluoro phenyl	563
5	2-methoxy phenyl	575
6	2-phenylethyl	573
7	3,4-methylenedioxy phenyl	589

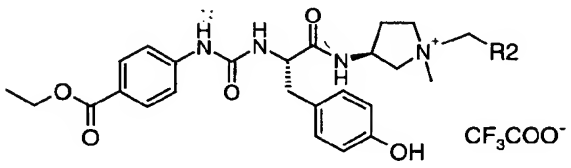
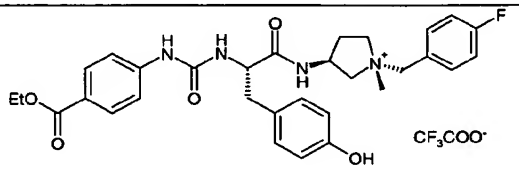
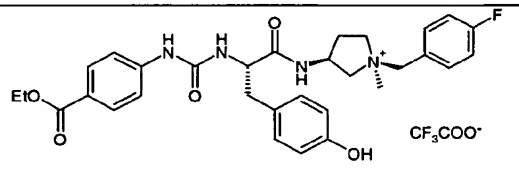
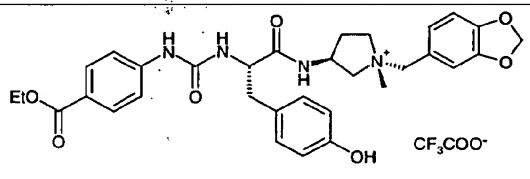
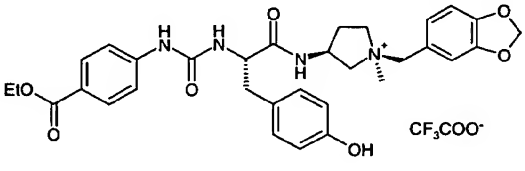


Table 2

Example	R2	MS [M]+
8	4-cyano phenyl	570
9	4-fluoro phenyl	563
10	3,4-dimethoxy phenyl	605
11	3,4-methylenedioxy phenyl	589
12	cyclopropyl	509
13	3-hydroxy phenyl	561
14	3-fluoro phenyl	563
15	3-cyano phenyl	570
16	4-acetyl phenyl	587
17	4-acetamido phenyl	602
18	H	469
19	4-carboxy phenyl	589

20	4-chloro phenyl	579
21	3-chloro phenyl	579

Table 3

Example	Compound	MS [M]+
22		563
23		563
24		589
25		589

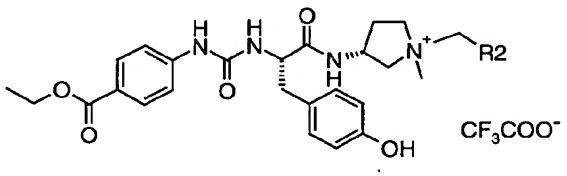


Table 4

Example	R2	MS [M]+
26	4-hydroxy phenyl	561
27	4-cyano phenyl	570
28	4-fluoro phenyl	563
29	3,4-dimethoxy phenyl	605
30	3,4-methylenedioxy phenyl	589

31	cyclopropyl	509

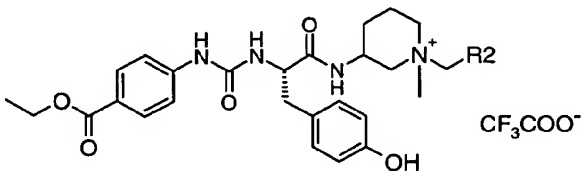


Table 5

Example	R2	MS [M]+
32	4-hydroxy phenyl	575
33	4-cyano phenyl	584
34	4-fluoro phenyl	577
35	3,4-dimethoxy phenyl	619
36	3,4-methylenedioxy phenyl	603
37	cyclopropyl	523

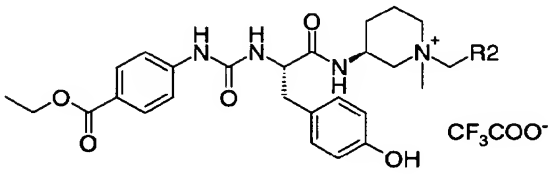


Table 6

Example	R2	MS [M]+
38	4-fluoro phenyl	577
39	3,4-methylenedioxy phenyl	603
40	4-hydroxy phenyl	575
41	3-chloro phenyl	593
42	3,4-dimethoxy phenyl	619
43	3-hydroxy phenyl	575
44	4-chloro phenyl	593
45	cyclopropyl	523

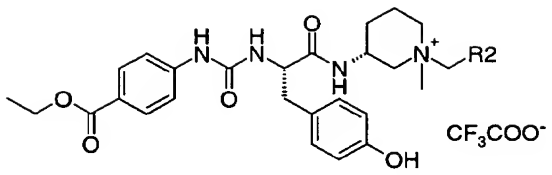


Table 7

Example	R2	MS [M]+
46	4-fluoro phenyl	577
47	3,4-methylenedioxy phenyl	603
48	3-chloro phenyl	593
49	3-hydroxy phenyl	575
50	4-chloro phenyl	593

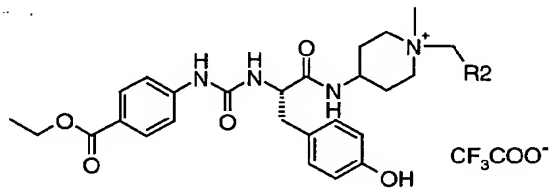


Table 8

Example	R2	MS [M]+
51	4-hydroxy phenyl	575
52	4-cyano phenyl	584
53	4-fluoro phenyl	577
54	3,4-dimethoxy phenyl	619
55	3,4-methylenedioxy phenyl	603
56	cyclopropyl	523

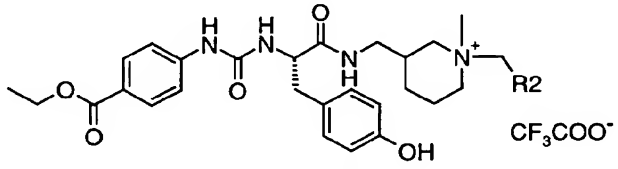


Table 9

Exampl	R2	MS [M]+

57	4-hydroxy phenyl	589
58	4-cyano phenyl	598
59	4-fluoro phenyl	591
60	3,4-dimethoxy phenyl	633
61	3,4-methylenedioxy phenyl	617
62	cyclopropyl	537

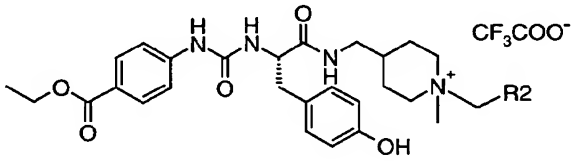


Table 10

Example	R2	MS [M]+
63	4-hydroxy phenyl	589
64	4-cyano phenyl	598
65	4-fluoro phenyl	591
66	3,4-dimethoxy phenyl	633
67	3,4-methylenedioxy phenyl	617
68	cyclopropyl	537

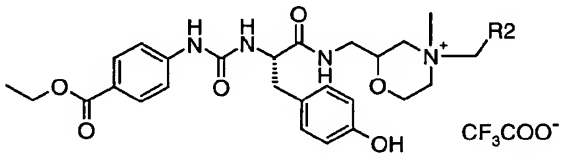


Table 11

Example	R2	MS [M]+
69	4-hydroxy phenyl	591
70	4-cyano phenyl	600
71	4-fluoro phenyl	593
72	3,4-dimethoxy phenyl	635
73	3,4-methylenedioxy phenyl	619
74	cyclopropyl	539

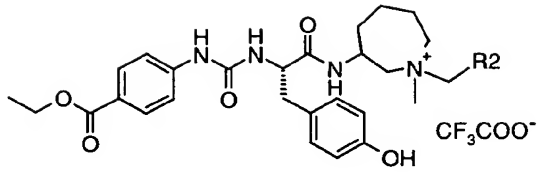


Table 12

Example	R2	MS [M]+
75	4-hydroxy phenyl	589
76	4-cyano phenyl	598
77	4-fluoro phenyl	591
78	3,4-dimethoxy phenyl	633
79	3,4-methylenedioxy phenyl	617
80	cyclopropyl	537

Proceeding in a similar manner as described in example 1, but replacing Fmoc-Try(tBu)-OH with other Fmoc protected amino acids and/or replacing 4-hydroxybenzaldehyde with the appropriate aldehydes, the compounds listed in Tables 13 - 15 were prepared.

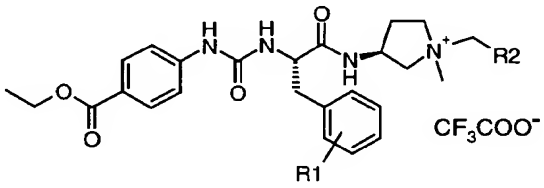


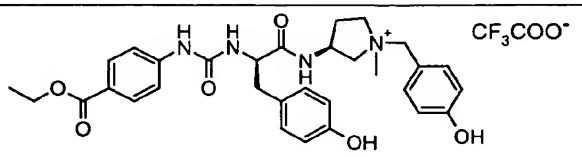
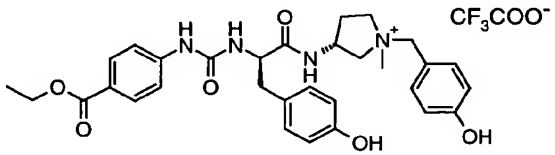
Table 13

Example	R1	R2	MS [M]+
81	4-chloro	3,4-methylenedioxy phenyl	607
82	4-phenylcarbonyl	3,4-methylenedioxy phenyl	677
83	4-methoxy	3,4-methylenedioxy phenyl	603
84	4-fluoro	3,4-methylenedioxy phenyl	591
85	4-phenyl	3,4-methylenedioxy phenyl	649

86	4-chloro	4-fluoro phenyl	581
87	4-phenylcarbonyl	4-fluoro phenyl	651
88	4-methoxy	4-fluoro phenyl	577
89	4-fluoro	4-fluoro phenyl	565
90	4-phenyl	4-fluoro phenyl	623
91	4-methyl	3,4-methylenedioxy phenyl	587
92	4-bromo	3,4-methylenedioxy phenyl	651
93	3,4-dichloro	3,4-methylenedioxy phenyl	641
94	3-chloro	3,4-methylenedioxy phenyl	607
95	4-cyano	3,4-methylenedioxy phenyl	598
96	2-chloro	3,4-methylenedioxy phenyl	607
97	4-trifluoromethyl	3,4-methylenedioxy phenyl	641
98	3-cyano	3,4-methylenedioxy phenyl	598
99	3,4-dimethoxy	3,4-methylenedioxy phenyl	633
100	4-methyl	4-fluoro phenyl	561
101	4-bromo	4-fluoro phenyl	625
102	3,4-dichloro	4-fluoro phenyl	615
103	3-chloro	4-fluoro phenyl	581
104	4-cyano	4-fluoro phenyl	572
105	2-chloro	4-fluoro phenyl	581
106	4-trifluoromethyl	4-fluoro phenyl	615
107	3-cyano	4-fluoro phenyl	572
108	3,4-dimethoxy	4-fluoro phenyl	607
109	4-amino	3,4-methylenedioxy phenyl	588
110	4-amino	4-fluoro phenyl	562
111	4-carboxyl	4-fluoro phenyl	590

Table 14

Example	Compound	MS $[M]^+$

112		561
113		561

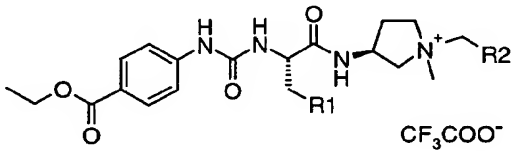


Table 15

Example	R1	R2	MS [M]+
114	2-naphthyl	3,4-methylenedioxy phenyl	623
115	1-naphthyl	3,4-methylenedioxy phenyl	623
116	2-naphthyl	4-fluoro phenyl	597
117	1-naphthyl	4-fluoro phenyl	597

Proceeding in a similar manner as described in example 1, but replacing 4-hydroxybenzaldehyde with the appropriate aldehydes and replacing iodomethane with other alkyl halides, the compounds listed in Table 16 were prepared.

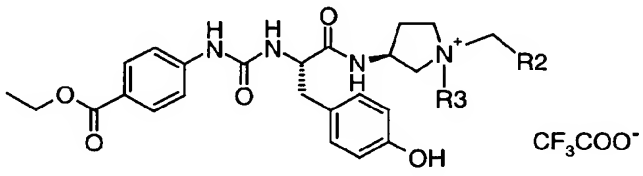


Table 16

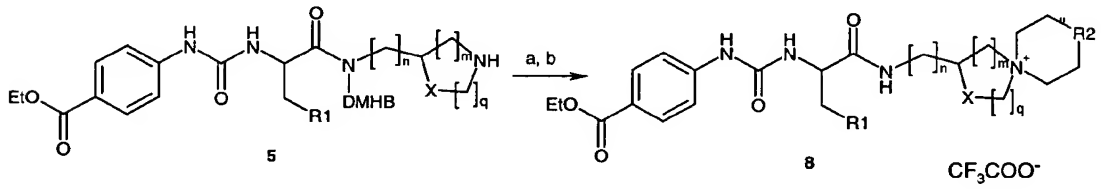
Example	R2	R3	MS [M]+
118	4-fluoro phenyl	ethyl	577
119	4-fluoro phenyl	n-propyl	591

120	4-fluoro phenyl	2-propen-1-yl	589
121	4-fluoro phenyl	4-fluorobenzyl	657
122	4-cyano phenyl	ethyl	584
123	4-cyano phenyl	n-propyl	598
124	4-cyano phenyl	2-propen-1-yl	596
125	4-cyano phenyl	4-cyanobenzyl	671
126	4-chloro phenyl	ethyl	593
127	4-chloro phenyl	n-propyl	607
128	4-chloro phenyl	2-propen-1-yl	605
129	4-chloro phenyl	4-chlorobenzyl	689

Preparation 2

Resin-bound secondary amines **5** were treated with alkyl dihalides to give the corresponding resin-bound quaternary ammonium salts, which were then cleaved with 50% trifluoroacetic acid in 1,2-dichloroethane to afford targeted compounds **8** (Scheme 2).

Scheme 2



Conditions: a) alkyl dihalides, acetonitrile, 50 °C; b) 50% trifluoroacetic acid in 1,2-dichloroethane, rt.

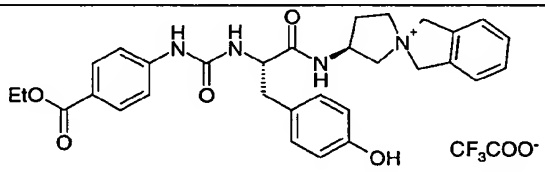
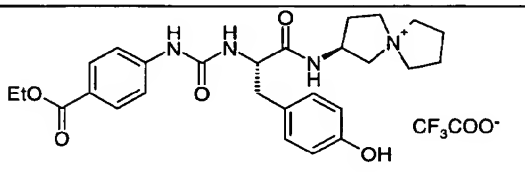
Example 130

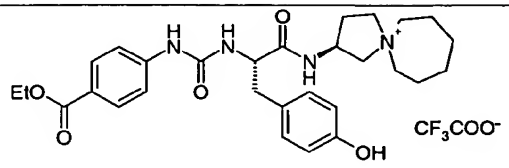
Preparation of (2*S*)-2-({*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosyl}amino)-5-azoniaspiro[4.5]decane trifluoroacetate

To 200 mg (0.178 mmol) of resin **1c** (DMHB resin-bound ethyl 4-{[({(1*S*)-1-({4-[(1,1-dimethylethyl)oxy]phenyl}methyl)-2-oxo-2-[(3*S*)-3-pyrrolidinylamino]ethyl}amino)carbonyl]amino}benzoate) was added 5 mL (36.7 mmol) of 1,5-dibromopentane. The mixture was shaken at 50 °C for overnight. After washing with methylene chloride (5x 6 mL), the resin was dried in vacuum oven at 35 °C for 24 h. The dry resin was treated with 4 mL of 50% trifluoroacetic acid in dichloroethane at rt for 1 h. After the cleavage solution was collected, the resin was treated with another 4 mL of 50% trifluoroacetic acid in dichloroethane at rt for 30 min. The combined cleavage solutions were concentrated *in vacuo*. The residue was purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce (2*S*)-2-({*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosyl}amino)-5-azoniaspiro[4.5]decane trifluoroacetate as a white powder (45 mg, 49% over 9 steps): MS (ESI) 509 $[M]^+$.

Proceeding in a similar manner as described in example 130, but replacing 1,5-dibromopentane with the appropriate alkyl dihalides, the compounds listed in Table 17 were prepared.

Table 17

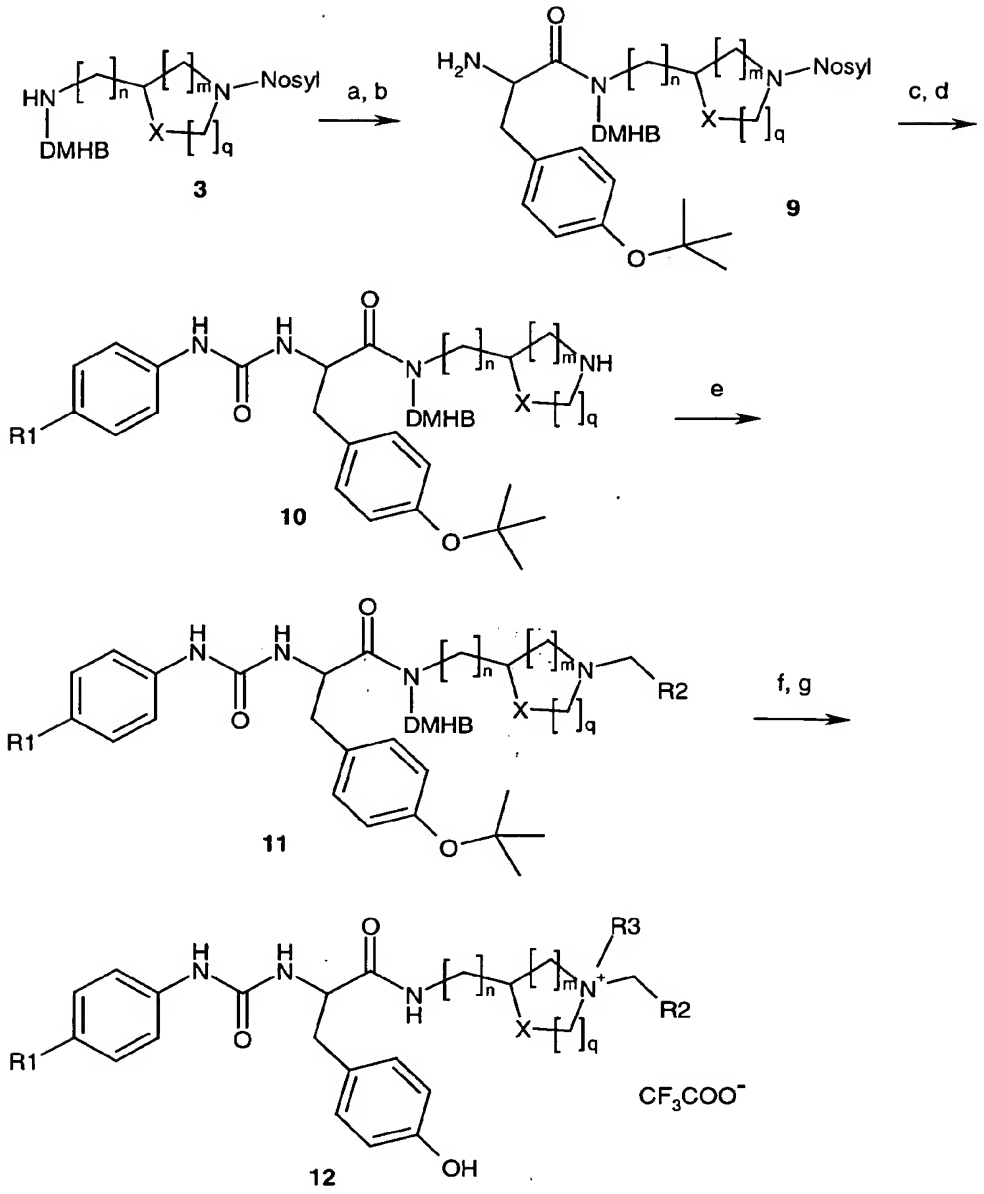
Example	Compound	MS $[M]^+$
131		543
132		495

133		523

Preparation 3

Resin-bound amines **3** were prepared in the same way as described in preparation 1. Reactions of **3** with Fmoc-Try(tBu)-OH, followed by removal of the Fmoc protecting group, provided resin-bound intermediates **9**. A variety of 4-substituted anilines were reacted with 1,1'-carbonyldiimidazole to give the intermediates which in turn were reacted with **9** to afford the corresponding resin-bound ureas. The ureas were subsequently treated with potassium carbonate and thiophenol to give secondary amines **10**. Reductive amination of **10** with appropriate aldehydes produced resin-bound tertiary amines **11**. Amines **11** were then reacted with alkyl halides (R3Z) to give the corresponding resin-bound quaternary ammonium salts, which were treated with 50% trifluoroacetic acid in 1,2-dichloroethane to afford targeted compounds **12** (Scheme 3).

Scheme 3



Conditions: a) Fmoc-Try(tBu)-OH, 1,3-diisopropylcarbodiimide, 1-hydroxy-7-azabenzotriazole, 1-methyl-2-pyrrolidinone, rt; b) 20% piperidine in 1-methyl-2-pyrrolidinone, rt; c) (R1)PhNH$_2$, 1,1'-carbonyldiimidazole,diisopropylethylamine, 1,2-dichloroethane, rt; d) K_2CO_3, PhSH, 1-methyl-2-pyrrolidinone, rt; e) R2CHO, Na(OAc)$_3$BH, 10% acetic acid in 1-methyl-2-pyrrolidinone, rt; f) R3Z, acetonitrile, rt; g) 50% trifluoroacetic acid in 1,2-dichloroethane, rt.

Exampl 134

Pr paration of *N*-{(3*S*)-1-[(3-cyanophenyl)methyl]-1-m thyl-3-pyrrolidiniumyl}-*N*-[({4-[(cyclopropylamino)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate

To a mixture of 35 mg (0.2 mmol) of 4-amino-cyclopropylbenzamide in 0.5 mL of anhydrous 1,2-dichloroethane was added 32 mg (0.2 mmol) of 1,1'-carbonyldiimidazole, followed by an addition of 35 uL (0.2 mmol) of diisopropylethylamine. After the resulting mixture was shaken at rt for 0.5 h, it was pipetted to a mixture of 50 mg (0.04 mmol, 0.8 mmol/g) of example **1b** (DMHB resin bound *O*-(1,1-dimethylethyl)-*N*-{(3*S*)-1-[(2-nitrophenyl)sulfonyl]-3-pyrrolidinyl}-L-tyrosinamide) in 1,2-dichloroethane (0.5 mL). After the resulting mixture was shaken at rt for 24 h, the resin was washed with CH_2Cl_2 (3 x 1 mL), CH_2Cl_2/MeOH (1:1, 3 x 1 mL), MeOH (3 x 1 mL) and CH_2Cl_2 (3 x 10mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 637 $[M+H\text{-}tBu]^+$.

To a mixture of the above dry resin (0.04 mmol) in 1 mL of 1-methyl-2-pyrrolidinone was added 41.5 mg (0.3 mmol) of K_2CO_3 and 15.4 µL (0.15 mmol) of PhSH. After the resulting mixture was shaken at rt for 2 h, the resin was washed with DMF (3 x 10 mL), H_2O (3 x 10 mL), DMF (3 x 10 mL), CH_2Cl_2/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 452 $[M+H\text{-}tBu]^+$.

To a mixture of the above dry resin (0.04 mmol) in 1 mL of 10% HOAc in anhydrous 1-methyl-2-pyrrolidinone solution was added 79 mg (0.6 mmol) of 3-cyanobenzaldehyde and 127.2 mg (0.6 mmol) of sodium triacetoxyborohydride. After the resulting mixture was shaken at rt for 24 h, the resin was washed with DMF (3 x 10 mL), CH_2Cl_2/MeOH (1:1, 3 x 10 mL)

and MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 ^{o}C for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 567 $[M+H-tBu]^{+}$.

To a mixture of the above dry resin (0.04 mmol) in 1 mL of anhydrous acetonitrile was added 18.7 µL 0.3 mmol) of iodomethane. After the mixture was shaken at rt for 16 h, the resin was washed with DMF (3 x 10 mL), CH_2Cl_2/MeOH (1:1, 3 x 10 mL), MeOH (3 x 10 mL) and CH_2Cl_2 (3x10mL). The resulting resin was dried in vacuum oven at 35 ^{o}C for 24 h. The dry resin was treated with 2 mL of 50% trifluoroacetic acid in dichloroethane at rt for 2h. After the cleavage solution was collected, the resin was treated with another 2 mL of 50% trifluoroacetic acid in dichloroethane at rt for 10min. The combined cleavage solutions were concentrated *in vacuo*. The residue was purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce *N*-{(3*S*)-1-[(3-cyanophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-[({4-[(cyclopropylamino)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate (white powder, 16 mg, 57% over 10 steps): MS (ESI) 581 $[M]^{+}$.

Proceeding in a similar manner as described in example 134, but replacing 4-amino-cyclopropylbenzamide with the appropriate anilines, and/or replacing 3(*S*)-(-)-(*tert*-butoxycarbonyl-amino)pyrrolidine with 3(*S*)-(-)-(*tert*-butoxycarbonyl-amino)piperidine, and/or replacing 3-cyanobenzaldehyde with the appropriate aldehydes, the compounds listed in Tables 18 - 23 were prepared.

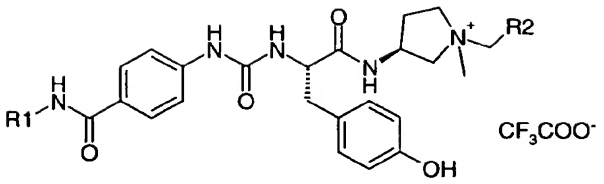


Table 18

Example	R1	R2	MS [M]+
135	cyclopropyl	4-hydroxy phenyl	572
136	cyclopropyl	3-chloro phenyl	591
137	cyclopropyl	4-chloro phenyl	591
138	cyclopropyl	3,4-dimethoxy phenyl	616
139	cyclopropyl	3,4-methylenedioxy phenyl	600
140	cyclopropyl	4-fluoro phenyl	574
141	1-methylethyl	3-cyano phenyl	583
142	1-methylethyl	3-chloro phenyl	592
143	1-methylethyl	4-chloro phenyl	592
144	1-methylethyl	3,4-dimethoxy phenyl	618
145	1-methylethyl	3,4-methylenedioxy phenyl	602
146	1-methylethyl	4-fluoro phenyl	576
147	1-methylethyl	4-hydroxy phenyl	575
148	1-methylethyl	3-hydroxy phenyl	575

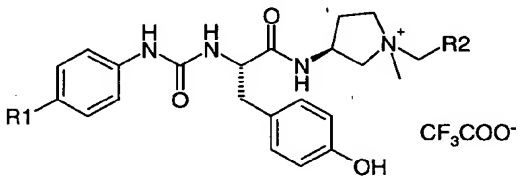
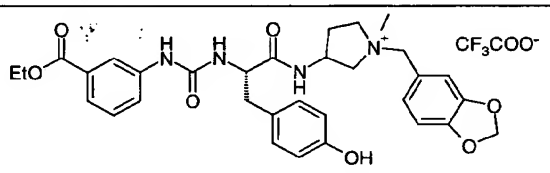


Table 19

Example	R1	R2	MS [M]+
149	(4-methylphenyl)oxy	3,4-methylenedioxy phenyl	623
150	(4-chlorophenyl)oxy	3,4-methylenedioxy phenyl	643
151	(4-methylphenyl)oxy	4-fluoro phenyl	597
152	(4-chlorophenyl)oxy	4-fluoro phenyl	617

153	acetyl	3,4-methylenedioxy phenyl	559
154	propanoyl	3,4-methylenedioxy phenyl	573
155	butanoyl	3,4-methylenedioxy phenyl	587
156	ethyloxy	3,4-methylenedioxy phenyl	561
157	cyano	3,4-methylenedioxy phenyl	542
158	acetyl	4-fluoro phenyl	533
159	propanoyl	4-fluoro phenyl	547
160	butanoyl	4-fluoro phenyl	561
161	ethyloxy	4-fluoro phenyl	535
162	cyano	4-fluoro phenyl	516

Table 20

Example	Compound	MS [M]+
163		589

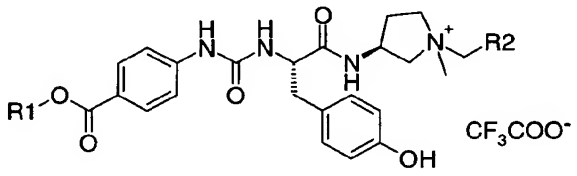


Table 21

Example	R1	R2	MS [M]+
164	methyl	4-fluoro phenyl	549
165	methyl	3,4-methylenedioxy phenyl	575
166	1-methylethyl	4-fluoro phenyl	577
167	1-methylethyl	3,4-methylenedioxy phenyl	603
168	1-methylethyl	4-hydroxy phenyl	575
169	1-methylethyl	3-chloro phenyl	593
170	1-methylethyl	3,4-dimethoxy phenyl	619

171	1-methylethyl	3-hydroxy phenyl	575
172	1-methylethyl	4-chloro phenyl	593
173	1-methylethyl	cyclopropyl	523
174	n-propyl	4-fluoro phenyl	577
175	n-propyl	3,4-methylenedioxy phenyl	603

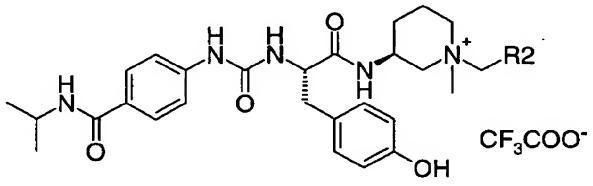


Table 22

Example	R2	MS [M]+
176	4-fluoro phenyl	590
177	3,4-methylenedioxy phenyl	616
178	4-hydroxy phenyl	588
179	3-chloro phenyl	606
180	3,4-dimethoxy phenyl	632
181	3-hydroxy phenyl	588

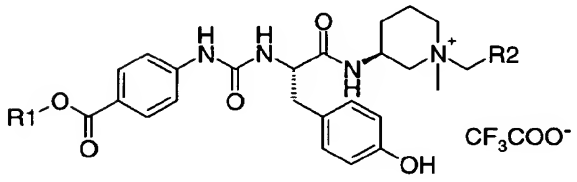


Table 23

Example	R1	R2	MS [M]+
182	methyl	4-fluoro phenyl	563
183	methyl	3,4-methylenedioxy phenyl	589
184	1-methylethyl	4-fluoro phenyl	591
185	1-methylethyl	3,4-methylenedioxy phenyl	617
186	1-methylethyl	4-hydroxy phenyl	589
187	1-methylethyl	3-chloro phenyl	607

188	1-methylethyl	3,4-dimethoxy phenyl	633
189	1-methylethyl	3-hydroxy phenyl	589
190	1-methylethyl	4-chloro phenyl	607
191	1-methylethyl	cyclopropyl	537
192	n-propyl	4-fluoro phenyl	591
193	n-propyl	3,4-methylenedioxy phenyl	617

Proceeding in a similar manner as described in example 134, but replacing 4-amino-cyclopropylbenzamide with the appropriate 1,2,4-oxadiazol anilines, and/or replacing 3(*S*)-(-)-(*tert*-butoxycarbonyl-amino)pyrrolidine with 3(*S*)-(-)-(*tert*-butoxycarbonyl-amino)piperidine and/or replacing 3-cyanobenzaldehyde with the appropriate aldehydes, the compounds listed in Tables 24 - 31 were prepared.

1,2,4-Oxadiazol anilines were prepared by reduction of nitrophenyl-1,2,4-oxadiazoles (Lin, Lang, *J. Heterocycl. Chem.* 1980, 17, 1273), which were prepared by cyclizing amidoximes obtained by reaction of nitriles with hydroxyamine (Diana, Volkots, et al. *J. Med.Chem.*1994, 37, 2421).

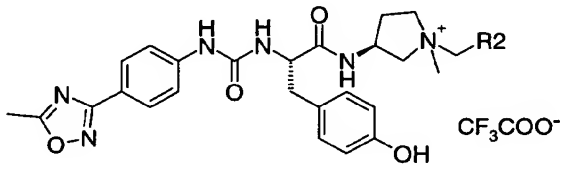


Table 24

Example	R2	MS [M]+
194	4-fluoro phenyl	573
195	3,4-methylenedioxy phenyl	599
196	3-hydroxy phenyl	571

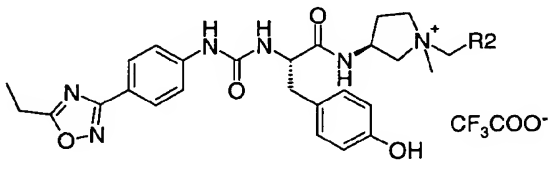


Table 25

Exampl	R2	MS [M]+
197	4-fluoro phenyl	587
198	3,4-methylenedioxy phenyl	613
199	3-hydroxy phenyl	585

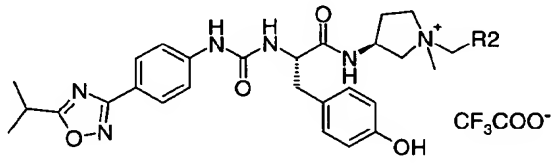


Table 26

Example	R2	MS [M]+
200	4-fluoro phenyl	603
201	3,4-methylenedioxy phenyl	627
202	3-hydroxy phenyl	599

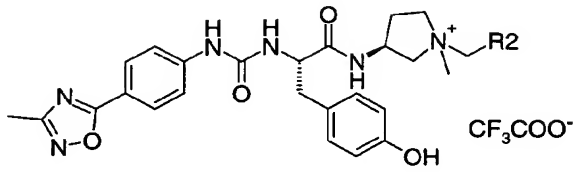


Table 27

Example	R2	MS [M]+
203	4-fluoro phenyl	573
204	3,4-methylenedioxy phenyl	599
205	3-hydroxy phenyl	571

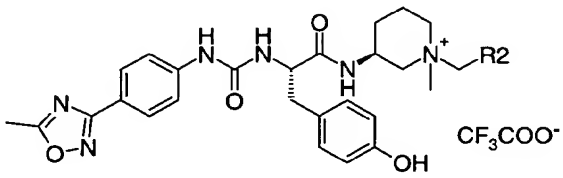


Table 28

Exampl	R2	MS [M]+
206	4-fluoro phenyl	587
207	3,4-methylenedioxy phenyl	613
208	3,4-dimethoxy phenyl	629
209	3-hydroxy phenyl	585

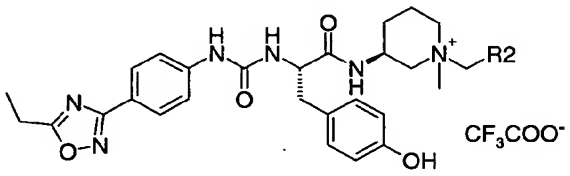


Table 29

Example	R2	MS [M]+
210	4-fluoro phenyl	601
211	3,4-methylenedioxy phenyl	627
212	3,4-dimethoxy phenyl	643
213	3-hydroxy phenyl	599

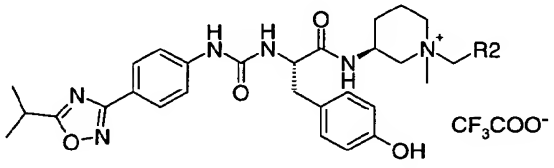


Table 30Example	R2	MS [M]+
214	4-fluoro phenyl	615
215	3,4-methylenedioxy phenyl	641
216	3,4-dimethoxy phenyl	657
217	3-hydroxy phenyl	613

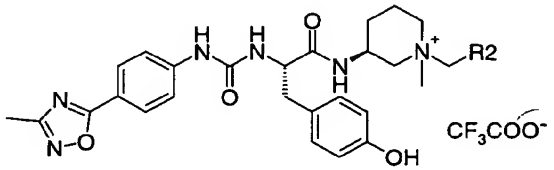


Table 31

Exampl	R2	MS [M]+
218	4-fluoro phenyl	587
219	3,4-methylenedioxy phenyl	613
220	3,4-dimethoxy phenyl	629
221	3-hydroxy phenyl	585

Proceeding in a similar manner as described in example 134, but replacing 4-amino-cyclopropylbenzamide with the appropriate anilines, and/or replacing 3(*S*)-(-)-(*tert*-butoxycarbonyl-amino)pyrrolidine with 3(*S*)-(-)-(*tert*-butoxycarbonyl-amino)piperidine and/or replacing 3-cyanobenzaldehyde with the appropriate aldehydes, and replacing iodomethane with appropriate halides, the compounds listed in Tables 32 - 34 were prepared.

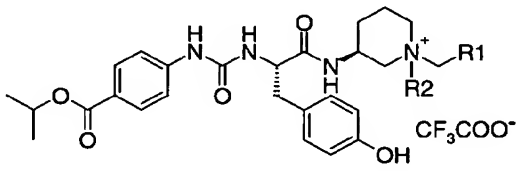


Table 32

Example	R1	R2	MS [M]+
222	3-hydroxyphenyl	n-propyl	617
223	3,4-methylenedioxyphenyl	n-propyl	645
224	3,4-dimethoxyphenyl	n-propyl	661
225	cyclopropyl	n-propyl	565
226	3-hydroxyphenyl	2-propen-1-yl	615
227	3,4-methylenedioxyphenyl	2-propen-1-yl	643
228	3,4-methoxyphenyl	2-propen-1-yl	659
229	cyclopropyl	2-propen-1-yl	563
230	cyclopropyl	cyclopropylmethyl	577
231	4-hydroxyphenyl	n-propyl	617

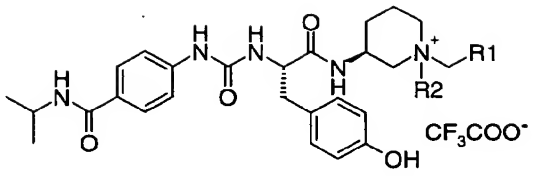
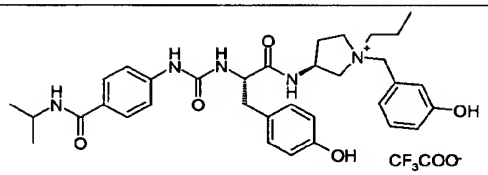
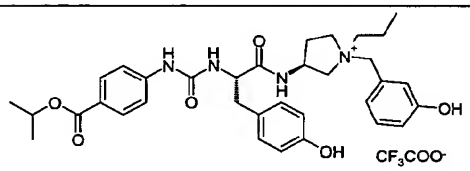
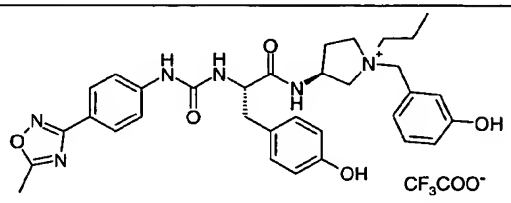
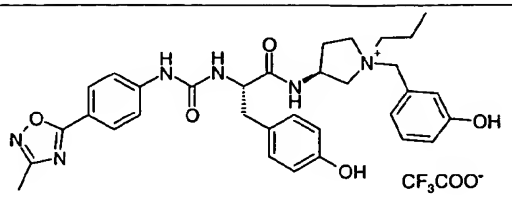


Table 33

Example	R1	R2	MS [M]+
232	3-hydroxyphenyl	n-propyl	616
233	3,4-methylenedioxyphenyl	n-propyl	644
234	3,4-methoxyphenyl	n-propyl	660
235	cyclopropyl	n-propyl	564
236	3-hydroxyphenyl	2-propen-1-yl	614
237	3,4-methylenedioxyphenyl	2-propen-1-yl	642
238	3,4-methoxyphenyl	2-propen-1-yl	658
239	cyclopropyl	2-propen-1-yl	562
240	cyclopropyl	cyclopropylmethyl	576

Table 34

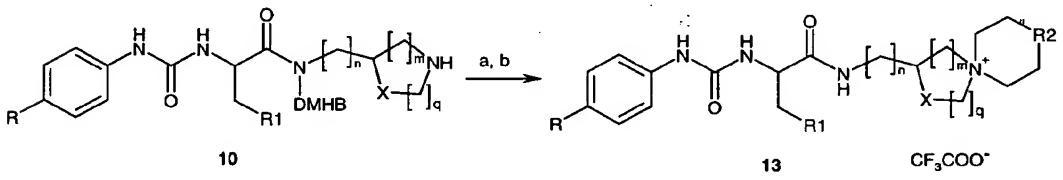
Example	Compound	MS [M]+
241		602
242		603
243		599

244		599

Preparation 4

Resin-bound secondary amines **10** were treated with alkyl dihalides to give the corresponding resin-bound quaternary ammonium salts, which were then cleaved with 50% trifluoroacetic acid in 1,2-dichloroethane to afford targeted compounds **13** (Scheme 4).

Scheme 4



10 **13**

Conditions: a) alkyl dihalides, acetonitrile, 75 °C; b) 50% trifluoroacetic acid in 1,2-dichloroethane, rt.

Example 245

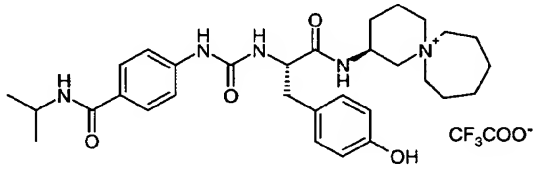
Preparation of (2*S*)-2-[(*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl) amino]carbonyl}-L-tyrosyl)amino]-6-azoniaspiro[5.6]dodecane trifluoroacetate

DMHB resin-bound 1-methylethyl 4-{[({(1*S*)-1-({4-[(1,1-dimethylethyl) oxy]phenyl}methyl)-2-oxo-2-[(3*S*)-3-piperidinylamino]ethyl}amino)carbonyl]amino}benzoate was prepared in the same way as described in example **134**. To 80 mg (0.36mmol/g, 0.029 mmol) of this resin in acetonitrile (6.4 mL) was added (0.488mL, 3.2 mmol) of 1,6-dibromohexane. The mixture was shaken at 75 °C for overnight. After washing with methylene chloride (5x 2 mL), the resin was dried in

vacuum oven at 35 °C for 24 h. The dry resin was treated with 2 mL of 50% trifluoroacetic acid in 1,2-dichloroethane at rt for 1 h. After the cleavage solution was collected, the resin was treated with another 2 mL of 50% trifluoroacetic acid in 1,2-dichloroethane at rt for 30 min. The combined cleavage solutions were concentrated *in vacuo*. The residue was purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce (2*S*)-2-[(*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl) amino]carbonyl}-L-tyrosyl)amino]-6-azoniaspiro[5.6]dodecane trifluoroacetate as a white powder (6.2 mg, 22% over 9 steps): MS (ESI) 551 $[M]^+$.

Proceeding in a similar manner as described in example 245, the compound listed in Table 35 was prepared.

Table 35

Example	Compound	MS $[M]^+$
246		550

BIOLOGICAL EXAMPLES

The inhibitory effects of compounds at the M_3 mAChR of the present invention are determined by the following *in vitro* and *in vivo* assays:

Analysis of Inhibition of R ceptor Activation by Calcium Mobilization:

1) 384-well FLIPR assay

A CHO (chinese hamster ovary) cell line stably expressing the human M3 muscarinic acetylcholine receptor is grown in DMEM plus 10% FBS, 2 mM Glutamine and 200 ug/ml G418. Cells are detached for maintenance and for plating in preparation for assays using either enzymatic or ion chelation methods. The day before the FLIPR (fluorometric imaging plate reader) assay, cells are detached, resuspended, counted, and plated to give 20,000 cells per 384 well in a 50 ul volume. The assay plates are black clear bottom plates, Becton Dickinson catalog number 35 3962. After overnight incubation of plated cells at 37 degrees C in a tissue culture incubator, the assay is run the next day. To run the assay, media are aspirated, and cells are washed with 1x assay buffer (145mM NaCl, 2.5mM KCl, 10mM glucose, 10mM HEPES, 1.2 mM $MgCl_2$, 2.5mM $CaCl_2$, 2.5mM probenecid (pH 7.4.) Cells are then incubated with 50ul of Fluo-3 dye (4uM in assay buffer) for 60 – 90 minutes at 37 degrees C. The calcium- sensitive dye allows cells to exhibit an increase in fluorescence upon response to ligand via release of calcium from intracellular calcium stores. Cells are washed with assay buffer, and then resuspended in 50ul assay buffer prior to use for experiments. Test compounds and antagonists are added in 25 ul volume, and plates are incubated at 37 degrees C for 5 -30 minutes. A second addition is then made to each well, this time with the agonist challenge, acetylcholine. It is added in 25 ul volume on the FLIPR instrument. Calcium responses are measured by changes in fluorescent units. To measure the activity of inhibitors / antagonists, acetylcholine ligand is added at an EC_{80} concentration, and the antagonist IC_{50} can then be determined using dose response dilution curves. The control antagonist used with M3 is atropine.

2) 96-well FLIPR assay

Stimulation of mAChRs expressed on CHO cells were analyzed by monitoring receptor-activated calcium mobilization as previously described .

CHO cells stably expressing M_3 mAChRs were plated in 96 well black wall/clear bottom plates. After 18 to 24 hours, media was aspirated and replaced with 100 µl of load media (EMEM with Earl's salts, 0.1% RIA-grade BSA (Sigma, St. Louis MO), and 4 µM Fluo-3-acetoxymethyl ester fluorescent indicator dye (Fluo-3 AM, Molecular Probes, Eugene, OR) and incubated 1 hr at 37° C. The dye-containing media was then aspirated, replaced with fresh media (without Fluo-3 AM), and cells were incubated for 10 minutes at 37° C. Cells were then washed 3 times and incubated for 10 minutes at 37° C in 100 µl of assay buffer (0.1% gelatin (Sigma), 120 mM NaCl, 4.6 mM KCl, 1 mM KH_2PO_4, 25 mM $NaHCO_3$, 1.0 mM $CaCl_2$, 1.1 mM $MgCl_2$, 11 mM glucose, 20mM HEPES (pH 7.4)). 50 µl of compound ($1x10^{-11}$ – $1x10^{-5}$ M final in the assay) was added and the plates were incubated for 10 min. at 37° C. Plates were then placed into a fluorescent light intensity plate reader (FLIPR, Molecular Probes) where the dye loaded cells were exposed to excitation light (488 nm) from a 6 watt argon laser. Cells were activated by adding 50 µl of acetylcholine (0.1-10 nM final), prepared in buffer containing 0.1% BSA, at a rate of 50 µl/sec. Calcium mobilization, monitored as change in cytosolic calcium concentration, was measured as change in 566 nm emission intensity. The change in emission intensity is directly related to cytosolic calcium levels . The emitted fluorescence from all 96 wells is measured simultaneously using a cooled CCD camera. Data points are collected every second. This data was then plotting and analyzed using GraphPad PRISM software.

Methacholine-induced bronchoconstriction

Airway responsiveness to methacholine was determined in awake, unrestrained BalbC mice ($n = 6$ each group). Barometric plethysmography was used to measure enhanced pause (Penh), a unitless measure that has been shown to correlate with the changes in airway resistance that occur during bronchial challenge with methacholine. Mice were pretreated with 50 µl of compound (0.003-10 µg/mouse) in 50 µl of vehicle (10% DMSO)

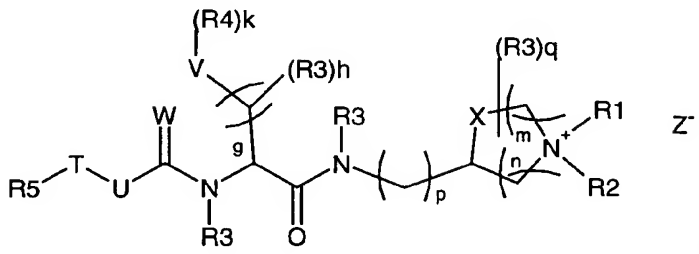
intranasally, and were then placed in the plethysmography chamber. Once in the chamber, the mice were allowed to equilibrate for 10 min before taking a baseline Penh measurement for 5 minutes. Mice were then challenged with an aerosol of methacholine (10 mg/ml) for 2 minutes. Penh was recorded continuously for 7 min starting at the inception of the methacholine aerosol, and continuing for 5 minutes afterward. Data for each mouse were analyzed and plotted by using GraphPad PRISM software.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A compound according to Formula I herein below:



(I)

wherein

When X is carbon, n is 1, 2, or 3; m is 1, 2, or 3; p is 0, 1, or 2;

When X is oxygen, n is 1; m is 2; p is 1 or 2;

W is O, S, or NH;

U is NR3, O, or bond;

R3 is selected from the group consisting of hydrogen, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, unsubstituted or substituted phenyl, or unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl and C_3-C_8 cycloalkyl lower alkyl;

q is an integer from 0 to 7;

h is 0, 1, or 2;

g is 1, 2, or 3;

Z^- is selected from the group consisting of I^-, Br^-, Cl^-, F^-, $CF3COO^-$, mesylate, tosylate, and any other pharmaceutically acceptable counter ion;

V is selected from the group consisting of phenyl, thiophenyl, furanyl, pyridinyl, naphthyl, quinolinyl, indolyl, benzothiophenyl and benzofuranyl;

R4 is selected from the group consisting of hydrogen, hydroxy, amino, halo, cyano, trifluoromethyl, C_1-C_8 alkoxy, C_1-C_8 branched or unbranched

alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, COR6, COOR6, CONHR6, CON(R6)2, NHR6, N(R6)2, and G;

k is an integer from 0 to 5;

T is selected from the group consisting of an unsubstituted or substituted following group: phenyl, thiophenyl, furanyl, pyridinyl, naphthyl, quinolinyl, indolyl, benzothiophenyl, or benzofuranyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R5 is selected from the group consisting of COOR6, CONHR6, COR6, CON(R6)2, COG, unsubstituted or substituted oxadiazolyl, unsubstituted or substituted oxazolyl, unsubstituted or substituted imidazolyl, unsubstituted or substituted phenoxy, or cyano; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl, C_1-C_8 alkoxy, halo, hydroxy, amino, cyano and trifluoromethyl;

R6 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted phenyl C1-C3 lower alkyl, unsubstituted or substituted naphthyl, or unsubstituted or substituted naphthyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

G is selected from the group consisting of an unsubstituted or substituted following group: pyrrolidinyl, piperdinyl, dihydroindolyl, tetrohydroquinolinyl, morpholino, azetidinyl, hexahydroazepinyl, or octahydroazocinyl; wherein, when substituted, a group is substituted by one

or more radicals selected from the group consisting of C_1-C_8 alkoxy, hydroxy, amino, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R1 is selected from the group consisting of an unsubstituted or substituted following group: phenyl, phenyl C1-C6 lower alkyl, thiophenyl, thiophenyl C1-C6 lower alkyl, furanyl, furanyl C1-C6 lower alkyl, pyridinyl, pyridinyl C1-C6 lower alkyl, imidazolyl, imidazolyl C1-C6 lower alkyl, naphthyl, naphthyl C1-C6 lower alkyl, quinolinyl, quinolinyl C1-C6 lower alkyl, indolyl, indolyl C1-C6 lower alkyl, benzothiophenyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl, benzofuranyl C1-C6 lower alkyl, benzoimidazolyl, benzoimidazolyl C1-C6 lower alkyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl C_1-C_6 lower alkyl, or C_3-C_8 alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, phenoxy, phenyl C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl, pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinolinyl, quinolinyl C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl, benzothiophenyl, benzothiophenyl C1-C3 lower alkyl, benzofuranyl, benzofuranyl C1-C3 lower alkyl, COOH, COR6, COOR6, CONHR6, CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6, OCONHR6, NHCOR6, N(R6)COR6, NHCOOR6 and NHCONHR6;

R2 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, C_3-C_8 alkenyl, unsubstituted or substituted phenyl, or unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy,

halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

or R1 and R2 is an unsubstituted or substituted following group:

$-(CH_2)_j-$, or $-(CH_2)_i$-Phenyl-$(CH_2)_i-$; wherein, j is an integer from 3 to 8; I is an integer from 1 to 3; when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

2. A compound according to claim 1 wherein:

When X is carbon, n is 1, 2, or 3; m is 1, 2, or 3; p is 0, or 1;

When X is oxygen, n is 1; m is 2; p is 1;

W is O;

U is NR3;

R3 is selected from the group consisting of hydrogen, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, and phenyl C1-C3 lower alkyl;

q is 0;

h is 0;

g is 1;

Z^- is selected from the group consisting of I^-, Br^-, Cl^-, F^-, $CF3COO^-$, mesylate, tosylate, or any other pharmaceutically acceptable counter ion;

V is selected from the group consisting of phenyl, thiophenyl, furanyl, naphthyl, benzothiophenyl or benzofuranyl;

R4 is selected from the group consisting of hydrogen, hydroxy, amino, halo, cyano, trifluoromethyl, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, phenylcarbonyl;

k is an integer from 1 to 5;

T is selected from the group consisting of an unsubstituted or substituted following group: phenyl, thiophenyl, furanyl, naphthyl, benzothiophenyl, or benzofuranyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R5 is selected from the group consisting of COOR6, CONHR6, COR6, CON(R6)2, COG, unsubstituted or substituted oxadiazolyl, unsubstituted or substituted phenoxy, or cyano; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl and trifluoromethyl;

R6 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, naphthyl, or naphthyl C1-C3 lower alkyl;

G is selected from the group consisting of pyrrolidinyl, piperdinyl, dihydroindolyl, tetrohydroquinolinyl, morpholino, azetidinyl, hexahydroazepinyl, and octahydroazocinyl;

R1 is selected from the group consisting of an unsubstituted or substituted following group: phenyl C1-C6 lower alkyl, thiophenyl C1-C6 lower alkyl, furanyl C1-C6 lower alkyl, pyridinyl C1-C6 lower alkyl, imidazolyl C1-C6 lower alkyl, naphthyl C1-C6 lower alkyl, quinolinyl C1-C6 lower alkyl, indolyl C1-C6 lower alkyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl C1-C6 lower alkyl, benzoimidazolyl C1-C6 lower alkyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl C_1-C_6 lower alkyl, or C_3-C_8 alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, phenoxy, phenyl C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C_1-C_8

branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl, pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinolinyl, quinolinyl C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl, benzothiophenyl, benzothiophenyl C1-C3 lower alkyl, benzofuranyl, benzofuranyl C1-C3 lower alkyl, COOH, COR6, COOR6, CONHR6, CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6, OCONHR6, NHCOR6, N(R6)COR6, NHCOOR6 and NHCONHR6;

R2 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, C_3-C_8 alkenyl, or unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

or R1 and R2 is $-(CH_2)_j-$, or $-(CH_2)_i$-Phenyl-$(CH_2)_i-$; wherein, j is an integer from 3 to 8; i is an integer from 1 to 3.

3. A compound according to claim 2 wherein:

X is carbon;

n is 1, or 2;

m is 1, 2, or 3;

p is 0, or 1;

W is O;

U is NR3;

R3 is hydrogen;

q is 0;

h is 0;

g is 1;

Z^- is selected from the group consisting of I^-, Br^-, Cl^-, F^-, $CF3COO^-$, mesylate, tosylate, and any other pharmaceutically acceptable counter ion;

V is selected from the group consisting of phenyl, or naphthyl;

R4 is selected from the group consisting of hydroxy, amino, halo, cyano, trifluoromethyl, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, phenylcarbonyl;

k is an integer from 1 to 3;

T is selected from the group consisting of unsubstituted or substituted phenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R5 is selected from the group consisting of COOR6, CONHR6, COR6, CON(R6)2, COG, unsubstituted or substituted oxadiazolyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R6 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, and C_3-C_8 cycloalkyl lower alkyl;

G is selected from the group consisting of pyrrolidinyl, piperdinyl, dihydroindolyl, tetrohydroquinolinyl, morpholino, azetidinyl, hexahydroazepinyl, and octahydroazocinyl;

R1 is selected from the group consisting of an unsubstituted or substituted following group: phenyl C1-C6 lower alkyl, thiophenyl C1-C6 lower alkyl, furanyl C1-C6 lower alkyl, pyridinyl C1-C6 lower alkyl, imidazolyl C1-C6 lower alkyl, naphthyl C1-C6 lower alkyl, quinolinyl C1-C6 lower alkyl, indolyl C1-C6 lower alkyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl C1-C6 lower alkyl, benzoimidazolyl C1-C6 lower alkyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl C_1-C_6 lower alkyl, or C_3-C_8 alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, phenoxy,

phenyl C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl, pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinolinyl, quinolinyl C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl, benzothiophenyl, benzothiophenyl C1-C3 lower alkyl, benzofuranyl, benzofuranyl C1-C3 lower alkyl, COOH, COR6, COOR6, CONHR6, CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6 and NHCOR6;

R2 is C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, or C_3-C_8 alkenyl;

or R1 and R2 is $-(CH_2)_j-$, or $-(CH_2)_i$-Phenyl-$(CH_2)_i-$; wherein, j is an integer from 3 to 7; i is an integer from 1 to 2.

4. A compound according to claim 1 selected from the group consisting of:

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{1-[(4-hydroxyphenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{1-[(4-fluorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(4-hydroxyphenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;
N-[(3*S*)-1-(cyclopropylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;
N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-pyrrolidiniumyl)-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;
N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl}-L-tyrosinamide trifluoroacetate;
N-[1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;
N-(1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;
N-[1-(cyclopropylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;
N-{[1-(cyclopropylmethyl)-1-methyl-4-piperidiniumyl]methyl}-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;
N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate;
N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(3-fluorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate;
N-{(3*S*)-1-[(3-cyanophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;
N-((3*S*)-1-{[4-(acetylamino)phenyl]methyl}-1-methyl-3-pyrrolidiniumyl)-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;
N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(1*R*,3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(1*S*,3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[(1*R*,3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[(1*S*,3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-4-chloro-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-phenylalaninamide trifluoroacetate;

(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-{[*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-3-(2-naphthalenyl)-L-alanyl]amino}-1-methylpyrrolidinium trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-4-(phenylcarbonyl)-L-phenylalaninamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-4-fluoro-L-phenylalaninamide trifluoroacetate;

(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-[((2*S*)-3-(4-biphenylyl)-2-{[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]amino}propanoyl)amino]-1-methylpyrrolidinium trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-4-methyl-L-phenylalaninamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-4-bromo-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-phenylalaninamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-3-chloro-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-phenylalaninamide trifluoroacetate;

4-amino-*N*-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-phenylalaninamide trifluoroacetate;

N-{(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-chlorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-pyrrolidiniumyl)-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-chlorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

(2*S*)-2-({*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosyl}amino)-5-azoniaspiro[4.5]decane trifluoroacetate;

(3'*S*)-3'-({*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosyl}amino)-1,3-dihydrospiro[isoindole-2,1'-pyrrolidine] trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-pyrrolidiniumyl)-*N*-[({4-[(cyclopropylamino)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-ethyl-1-[(4-fluorophenyl)methyl]-3-pyrrolidiniumyl}-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(4-fluorophenyl)methyl]-1-propyl-3-pyrrolidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-[(3*S*)-1-[(4-fluorophenyl)methyl]-1-(2-propen-1-yl)-3-pyrrolidiniumyl]-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-{[(4-butanoylphenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(2*S*)-5-azoniaspiro[4.4]non-2-yl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

(2*S*)-2-({*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosyl}amino)-5-azoniaspiro[4.6]undecane trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[({4-[(methyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[({4-[(propyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-({[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-({[4-(5-ethyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-({[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-chlorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(cyclopropylmethyl)-1-methyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-({[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-({[4-(5-ethyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-({[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-({[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-({[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-({[4-(5-ethyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-*N*-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1,1-bis(cyclopropylmethyl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1,1-bis(cyclopropylmethyl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

(2*S*)-2-[(*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosyl)amino]-6-azoniaspiro[5.6]dodecane trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-propyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-propyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-propyl-3-piperidiniumyl)-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-propyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-propyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-propyl-3-piperidiniumyl)-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-

methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-hydroxyphenyl)methyl]-1-propyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(cyclopropylmethyl)-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(cyclopropylmethyl)-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(cyclopropylmethyl)-1-propyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(cyclopropylmethyl)-1-propyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-({[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-({[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-({[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-({[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-L-tyrosinamide trifluoroacetate; and

N-[(3*S*)-1-(cyclopropylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

or any other pharmaceutically acceptable salt.

5. A compound according to claim 1 selected from the group consisting of:

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[({4-[(propyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-({[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-piperidiniumyl]-*N*-({[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-chlorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(cyclopropylmethyl)-1-methyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-pyrrolidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-methyl-3-pyrrolidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-({[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-({[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-({[4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-({[4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl]amino}carbonyl)-L-tyrosinamide trifluoroacetate;

N-({[4-(5-ethyl-1,2,4-oxadiazol-3-yl)phenyl]amino}carbonyl)-*N*-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1,1-bis(cyclopropylmethyl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1,1-bis(cyclopropylmethyl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

(2*S*)-2-[(*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosyl)amino]-6-azoniaspiro[5.6]dodecane trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-propyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-propyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-propyl-3-piperidiniumyl)-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-propyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-propyl-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-propyl-3-piperidiniumyl)-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[(3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-(2-propen-1-yl)-3-piperidiniumyl]-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-hydroxyphenyl)methyl]-1-propyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)oxy]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(4-fluorophenyl)methyl]-1-methyl-3-piperidiniumyl}-L-tyrosinamide trifluoroacetate;

N-{(3*S*)-1-[(3-chlorophenyl)methyl]-1-methyl-3-piperidiniumyl}-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-1-methyl-3-piperidiniumyl)-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;

N-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-*N*-{(3*S*)-1-[(3-hydroxyphenyl)methyl]-1-methyl-3-piperidiniumyl}-L-tyrosinamide trifluoroacetate; and
N-[(3*S*)-1-(cyclopropylmethyl)-1-methyl-3-piperidiniumyl]-*N*-[({4-[(ethyloxy)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide trifluoroacetate;
or any other pharmaceutically acceptable salt.

6. A pharmaceutical composition for the treatment of muscarinic acetylcholine receptor mediated diseases comprising a compound according to claim 1 and a pharmaceutically acceptable carrier thereof.

7. A method of inhibiting the binding of acetylcholine to its receptors in a mammal in need thereof comprising administering a safe and effective amount of a compound according to claim 1.

8. A method of treating a muscarinic acetylcholine receptor mediated disease, wherein acetylcholine binds to said receptor, comprising administering a safe and effective amount of a compound according to claim 1.

9. A method according to claim 8 wherein the disease is selected from the group consisting of chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema and allergic rhinitis.

10. A method according to claim 9 wherein administration is via inhalation via the mouth or nose.

11. A method according to claim 10 wherein administration is via a medicament dispenser selected from a reservoir dry powder inhaler, a multi-dose dry powder inhaler or a metered dose inhaler.

12. A method according to claim 11 wherein the compound is administered to a human and has a duration of action of 12 hours or more for a 1 mg dose.

13. A method according to claim 12 wherein the compound has a duration of action of 24 hours or more.

14. A method according to claim 13 wherein the compound has a duration of action of 36 hours or more.

ABSTRACT OF THE DISCLOSURE

Muscarinic Acetylcholine receptor antagonists and methods of using them are provided.